

Influenza A: The Zoonotic Connection

James Howell, DVM, MPH
Veterinary Epidemiologist

In 1997, 18 individuals contracted influenza A infection from poultry in the Hong Kong live bird market. This was the first known outbreak of human influenza attributed to an animal influenza virus since the 1976 “swine flu” episode. Since then, several human influenza cases have been identified as being caused by an avian influenza virus. The most serious outbreak is the ongoing outbreak of highly pathogenic avian influenza, influenza A (H5N1), which has affected the poultry industry in 10 Asian countries, with over 108 human cases and 54 deaths identified as of June 30, 2005. Because of the number of countries impacted and the number of human cases, there is much concern that this avian virus could be a precursor virus for an influenza pandemic.

Influenza is an acute viral disease of the respiratory tract and clinical descriptions of the disease in humans, swine, equine, and avian species are similar. In avian species, there is also an enteric component which may be a major feature of the infection and the major source of virus secretion. In general, influenza A subtypes that cause disease are species specific in mammals, but cross-over infections do occur. Serological epidemiology suggests that animal influenza subtypes introduced and adapted to human-to-human transmission have been the cause of past pandemics. Waterfowl, such as ducks and geese, are thought to be the original source of all the influenza A subtypes.

Influenza A virus subtypes are identified by two glycoproteins, hemagglutinin (H) and neuraminidase (N). Each influenza subtype is identified by its combination of H and N proteins. A limited number of subtypes has been linked to infections in mammalian species, but all combinations of the 15H and 9N glycoproteins studied have been identified in avian species, particularly wild waterfowl and shorebirds. Recently a new hemagglutinin (H16) was identified in European gulls. Based on serological studies, it is thought that only H1, H2, or H3 subtypes can infect humans or, at least, have been the only ones to infect humans during the past 100 years. These same studies provide information on the virus subtypes that have been associated with past pandemics (Table 1). Since 1997, there is increasing evidence that H5 or H7 viruses can also cause human illness (Table 2).

Table 1. Influenza Virus Subtypes Associated with Human Pandemics

| Pandemic Year | Influenza Virus Subtype |
|---------------|-------------------------------------|
| 1874 | H3N8 |
| 1890 | H2N2 |
| 1902 | H3N2 |
| 1918 | H1N1 “Spanish” |
| 1933 | H1N1 (first isolation of the virus) |
| 1947 | H1N1 |
| 1957 | H2N2 “Asian” |
| 1968 | H3N2 “Hong Kong” |
| 1976 | H1N1 “Swine” |
| 1977 | H1N1 + H3N2 “Russian” |

Table 2. Recent Human Cases Caused by Avian Influenza Subtypes

| Year | Subtype | Cases (Deaths) | Locations |
|---------|---------|----------------|-------------|
| 1997 | H5N1 | 18 (6) | Hong Kong |
| 1999 | H9N2 | 2 | Hong Kong |
| 2002 | H7N2 | 1 | Virginia |
| 2003 | H5N1 | 2 (1) | Hong Kong |
| 2003 | H7N7 | 69 (1) | Netherlands |
| 2003 | H7N2 | 1 | New York |
| 2003-05 | H5N1 | 107 (54) * | Asia |
| 2004 | H7N3 | 2 | Canada |
| 2004 | H9N2 | 1 | Hong Kong |
| 2004 | H10N7 | 2 | Egypt |

*World Health Organization, as of June 17, 2005

Wild waterfowl (especially ducks), shorebirds, and sea birds are a reservoir of avian influenza, with the various subtypes infecting their intestinal tracts without causing illness. At one lake site in Alaska over a four-year period, 108 isolations of eight different influenza A subtypes were identified from duck feces or from lake water.

Wild ducks secreting influenza virus can introduce virus to domestic ducks when wild ducks are allowed to intermingle or share ponds with domestic ducks. The virus can be found in both feces and the water in which they swim. Domestic ducks may or may not have clinical signs of influenza. In a four-year period in China and Hong Kong, 46 different H-N subtypes were identified in birds, 43 from domestic ducks. This finding is significant in that China raises a large number of ducks for human consumption and is located on a major flyway for migrating waterfowl, providing a ready source for human infections and distribution of viruses across a large area of the world.

In domestic poultry, influenza A subtypes are classified into two categories: low pathogenic avian influenza (LPAI) or high pathogenic avian influenza (HPAI). LPAI infections cause very mild infections, but HPAI infections often result in clinical influenza with high morbidity and mortality. The current H5N1 subtype present in Asia is a HPAI virus, and infections in poultry flocks have resulted in almost 100 percent mortality within 24 hours. HPAI infections have been associated with influenza H5 and H7 subtypes only, though not all H5 and H7 subtypes are highly pathogenic.

Until recently, it was thought that avian viruses only became infectious to humans by re-assortment of genetic material between avian viruses and viruses adapted for mammalian transmission, such as those infecting swine. The ability of swine influenza viruses to infect humans has been known since 1918, when an epidemic in swine coincided with the pandemic in humans. Opposing theories exist as to whether swine transmitted the infection to humans or humans transmitted the infection to swine. The influenza A (H1N1) subtype identified by serological epidemiology as causing the 1918 pandemic still circulates in swine populations around the world. Serological studies in swine have shown that, in the U.S., 25-33 percent of slaughter hogs show evidence of H1N1 infections. In 1976, an outbreak of "swine flu" at Fort Dix, New Jersey, caused by a similar H1N1 virus resulted in a number of human infections and one death. In 1988, an outbreak of swine influenza at a Wisconsin fair resulted in 19 of 25 swine exhibitors with clinical evidence of influenza having antibodies to the swine influenza virus. Three health care workers exposed to the ill swine exhibitors also developed influenza-like

illness. The current influenza A (H5N1) virus has been isolated from swine in Indonesia. The countries that are experiencing the current avian influenza outbreak also have large swine industries. Swine are often intermingled with ducks and chickens on farms, prompting concern that the potential for a re-assortment of viral genetic material in swine could lead to a virus better adapted to mammalian transmission.

In 1997, the first human cases of influenza A (H5N1) were identified in Hong Kong. This was the first time an avian subtype was known to have infected humans directly without adaptation to a lower mammalian host. The virus was first identified in Chinese geese in 1996. The human outbreak in 1997 was stopped by culling the entire poultry population in Hong Kong and disinfecting the live bird markets where transmission was taking place. Poultry outbreaks in Asia were recognized in 2001, 2002, and 2003. Since mid-December 2003, the following countries have been affected: Cambodia, China, Indonesia, Japan, Laos, Republic of Korea, Malaysia, Pakistan, Thailand, and Vietnam. Over 140 million birds have either died or have been destroyed in an effort to control the outbreak, and economic losses have approximated \$10-15 billion (U.S.). The agent is considered to be endemic in Asian domestic ducks; and since they are often asymptomatic, eliminating the virus will be problematic.

In January 2004, the first human cases associated with the current outbreak were reported from Thailand and Vietnam, followed by cases in Cambodia. To date, human cases have been related to the handling of sick poultry or exposure to infected blood or the consumption of undercooked chicken. There has been some evidence of case clustering, suggesting some person-to-person transmission for one or two generations of cases, but all clusters lead back to exposure to sick poultry. In addition to the H5N1 influenza cases recognized in humans, fatal H5N1 infections have been observed in tigers, leopards, and domestic cats after being fed raw meat from infected chickens.

Will this influenza A (H5N1) subtype virus, which has been sporadically infectious to people, be the novel virus for the next influenza pandemic? While the answer is unknown, there are a number of observations that suggest it has the potential to become more adaptable for human-to-human transmission.

- The virus is showing signs of genetic changes and difference in the clinical presentation in different geographic areas. There have been more clusters in northern Vietnam (8) than in southern Vietnam (2). It has been suggested that the virus circulating in northern Vietnam may be able to transmit from human to human more easily.
- The age range of cases is becoming wider. The average age of patients in northern Vietnam has increased from approximately 17 years of age in 2004 to approximately 31 years of age in 2005, while the approximate age of cases in southern Vietnam has remained almost unchanged at 15-18 years of age. The age range of infected persons has also increased from less than 1 year of age to greater than 80 years of age in northern Vietnam; while in southern Vietnam, the age range is still 2 to 40 years of age.
- In 2004, the case fatality rate in Thailand and Cambodia was 71-100 percent, but is now 34 percent in northern Vietnam. Additionally, there is evidence of several individuals having had asymptomatic infections. As a virus becomes more adapted

to humans, the case fatality rate will often decrease, allowing the virus more stable propagation in the human population.

Despite the above observations, scientists have been unable to document conclusive evidence that the virus has developed capabilities for efficient human transmission. In the meantime, the following steps may reduce the risk of virus adaptation for efficient human-to-human transmission and decrease the economic damage to the Asian poultry industry.

1. Continued surveillance of the disease in human populations to determine if efficient human-to-human transmission is occurring.
2. Continued steps to prevent, control, and eradicate HPAI:
 - Surveillance for early detection and reporting of outbreaks.
 - Enhanced bio-security of poultry farms and other facilities where poultry are housed or traded.
 - Control of movement of birds and poultry products that may contain virus, including prevention of infection entering previously uninfected geographic areas.
 - Rapid, humane destruction of infected birds and those potentially exposed.
 - Disposal of carcasses and potentially infective material in a manner to prevent further spread.
 - Vaccination of poultry where appropriate.

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